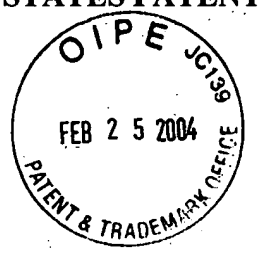
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE



In re application of:

Livshits et al.

Application No.: **09/466,935**

Filing Date: 20 December 1999

For: NOVEL GENE AND METHOD FOR PRODUCING L-AMINO ACIDS

Art Unit: 1652

Examiner: D.J. Steadman

Attorney Ref. No.: US-126O

BRIEF FOR APPELLANT

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

COMES NOW the Appellant to present this Brief in support of the appeal of the final rejections of Claims 37-48 in the above-captioned patent application. The Notice of Appeal having been timely filed on 25 August 2003, and a Petition with a one-month extension of time filed on November 25, this Brief is due to be filed on 25 February 2004 with a Petition for an additional three-months extension of time.

It is not believed that extensions of time are required, beyond those that may otherwise be provided for in accompanying documents. If, however, additional extensions of time are necessary to prevent abandonment of this application or dismissal of this appeal, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and the Commissioner is hereby authorized to charge fees necessitated by this paper, and to credit all refunds and overpayments, to the credit card authorized on the attached PTO-2038.

For the following reasons, Appellant respectfully submits that the final rejection of each of Claims 37-48 in this application is in error, and therefore respectfully requests reversal of the rejections.

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I. Real Party in Interest

The real party in interest is Ajinomoto Co., Inc, a corporation of Japan.

II. Related Appeals and Interferences

There are no related appeals or interferences.

III. Status of Claims

Claims 16-17 and 37-63 are pending. Claims 16-17 are in condition for allowance. Claims 37-48 stand finally rejected in the Advisory Actions dated 26 August 2003 and 30 January 2004, and are on appeal. Claims 49-63 are withdrawn from consideration as being drawn to a non-elected invention.

IV. Status of Amendments

All amendments to the claims have been entered, including the amendment after final filed on 26 August 2003.

V. Summary of Invention

The invention of the present application includes an isolated bacterium belonging to the genus *Escherichia*, wherein the bacterium is modified to increase an activity of a protein which makes the bacterium harboring the protein L-threonine-resistant and/or L-homoserine resistant in comparison to a wild-type *Escherichia* bacterium by increasing expression of a DNA coding for the protein, and wherein the protein comprises the amino acid sequence of SEQ ID NO: 4 (page 2, lines 11-19) or SEQ ID NO: 2 (page 3, line 25 to page 4, line 12) .

The invention further includes the above-described bacterium, wherein the bacterium is modified to increase an activity of the protein by increasing a copy number of a DNA coding for the protein (page 15, line 21 – page 16, line 11).

The invention further comprises the above-described bacterium wherein the bacterium is modified to increase an activity of the protein by substitution of a promoter sequence of the gene

coding for the protein with a promoter sequence which functions efficiently in a bacterium belonging to the genus *Escherichia* (page 14, line 21 – page 15, line 8).

The invention of the present application includes an isolated bacterium belonging to the genus *Escherichia*, wherein the bacterium is modified to increase an activity of a protein which makes the bacterium harboring the protein L-threonine-resistant and/or L-homoserine resistant in comparison to a wild-type *Escherichia* bacterium by increasing expression of a DNA coding for the protein, whereby the DNA is defined as a DNA which comprises the nucleotide sequence of nucleotide numbers 187 to 804 in SEQ ID NO 3., or a DNA which hybridizes to this DNA under stringent conditions, wherein the stringent conditions are conditions of washing performed at 60°C, and at a salt concentration of 1xSSC and 0.1% SDS (page 12, line 25 to page 14, line 11).

VI. Issues

A. Whether Claims 37-48 are unpatentable under 35 U.S.C. § 112, 1st paragraph, for lack of an adequate written description.

B. Whether Claims 37-48 are unpatentable under 35 U.S.C. § 112, 1st paragraph, for a lack of enablement in the specification concommitant with the scope of the claims.

VII. Grouping of Claims

A. For the rejections of Claims 37-48 under section 112, 1st paragraph, written description, all the claims stand or fall together.

B. For the rejections of Claims 37-48 under section 112, 1st paragraph, enablement, all the claims stand or fall together.

VIII. Argument

In the Office Action dated 26 August 2003 ("first Advisory Action"), beginning at page 2, Claims 37-48 were rejected under 35 U.S.C. § 112, 1st paragraph, for allegedly failing to be supported by a specification that includes an adequate written description of the claimed invention, and for allegedly failing to be supported by a specification that includes an enabling

disclosure. For at least the following reason, these rejections are in error and should be reversed.

A. Legal Standard

Because the written description requirement is separate and distinct from the enablement requirement, *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1562 (Fed. Cir. 1991), these issues are addressed separately.

A claimed invention is unpatentable due to the lack of a written description if the specification fails to "clearly convey the information that an applicant has invented the subject matter which is claimed", *In re Barker* 559 F.2d 588, 592 (CCPA 1977), or if possession of what applicant claims as the invention is not put in the public domain. See *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1566 (Fed. Cir. 1997), *cert. denied,* 523 U.S. 1089 (1998). To satisfy the written description requirement, possession must be shown; however possession alone does not cure the lack of a written description. *Enzo Biochem, Inc. v. Gen-Probe, Inc.,* 296 F.3d 1316, 1330 (Fed. Cir. 2002). For a claimed genus, the written description requirement may be satisfied through sufficient description of a representative number of species by disclosure of relevant identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or a combination of the above. See *Eli Lilly,* 119 F.3d at 1568. Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces. *See* M.P.E.P § 2163, II, A, 3, ii.

A claimed invention is unpatentable due to a non-enabling disclosure if the specification fails to describe how to make and how to use the invention. 35 U.S.C. § 112, 1st paragraph. The test for this standard is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art, without undue experimentation. *United States v. Telectronics, Inc.,* 857 F.2d 778, 785 (Fed. Cir. 1988). The seminal case in determining if a claim meets this standard is *In re Wands*, 858 F.2d 731, 737

(Fed. Cir. 1988), which promulgated a series of factors, set forth in office actions throughout the prosecution, see for example the Final Rejection of March 25, 2003, to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is 'undue.'

B. The rejection of Claims 37-48 under 35 U.S.C. § 112, 1st paragraph, written description, is in error

Claims 37-48 were rejected under section 112, 1st paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, as possession of the claimed invention.

Independent claim 37 recites an isolated bacterium belonging to the genus *Escherichia*. This bacterium is modified to increase an activity of a protein which makes the bacterium L-threonine resistant as compared to wild-type by increasing the expression of a DNA coding for the protein, and the literal scope of the claim limits the protein to the sequence of SEQ ID NO:4. The dependent claims further limit the features of claim 37 by reciting methods to increase the activity of a protein, such as increasing the copy number of the DNA coding for the protein (claim 38), or substitution of a more efficient promoter (claim 39). Claim 40, also dependent on claim 37, adds another protein for which the bacterium is modified to increase the activity, which renders the bacterium L-homoserine resistant as compared to the wild-type bacterium. This protein has the sequence set forth in SEQ ID NO:2, and further dependent claims also recite methods for increasing the protein activity, such as increasing the copy number of the DNA coding for the protein (claim 41), or substitution of a more efficient promoter (claim 42).

In explaining the written description rejection, the Examiner has alleged that "the specification fails to provide a sufficient description of the claimed genus of *Escherichia* bacteria as it merely describes the functional features of the genus without providing any definition of the structural features of the species within the genus" (paper number 18, page 5). Appellants

contend that the genus defined by claim 37 is actually a very small genus, in that the bacterium must be from the genus *Escherichia,* must be modified to increase the activity of a protein by increasing the expression of the DNA encoding the protein, the protein renders the bacterium harboring said protein L-threonine resistant as compared to wild-type, and the protein is limited to the amino acid sequence of SEQ ID NO:4. Appellants contend this is a very small genus; indeed, it appears that the Examiner fails to fully understand the limitations of the claims and the scope of the genus. Throughout the prosecution, the Examiner repeatedly states that the claimed genus encompasses *Escherchia* having <u>any modification</u> that results in increased protein activity and optionally enhanced gene expression (see, for example, paper no. 21, page 3). Actually the claimed genus encompasses not <u>any</u> modification to increase protein activity, but a modification to increase the protein activity of SEQ ID NO:4 by increasing the expression of the DNA encoding the protein of SEQ ID NO:4. Furthermore, this claimed protein activity increase can be easily screened for by measuring the L-threonine resistant activity, as this is also a limitation of the claim, and is exemplified in the specification at pages 30-31 in example 3.

The Examiner has repeatedly argued that appellants have failed to present a representative number of species, and most recently in the paper mailed January 30, 2004, stated that only two representative species are presented (see page 4). The paper goes on to state that only one representative species is presented. Regardless of the number of representative species, the Examiner's statement that the claimed genus is *Escherichia* bacteria having "<u>any</u> modification that results in increased DNA expression of a protein that makes the bacteria L-threonine resistant and optionally wherein increased DNA expression is a result of increased DNA copy number (by any modification) or promoter substitution (by any promoter)" (see page 4) is simply wrong, misstates the literal scope of the claims, and evinces a deep misunderstanding of the claimed subject matter. First, the claim is limited to not just any protein that makes the bacteria L-threonine resistant, but SEQ ID NO:4. This is a single species of protein and does not allow for variation or other species. Second, the skilled art worker must only determine which promoters might result in increased expression of the DNA which encodes SEQ ID NO:4. Selection of a promoter is a routine procedure, as evidenced by numerous

publications cited throughout prosecution. Third, alternatively the skilled art worker must select a multicopy vector to use for expression of the DNA which encodes SEQ ID NO:4, so as to increase the DNA expression. Again, this is a well-known method for DNA expression enhancement, again as documented in cited publications presented during prosecution (see documents D1 (WO92/10561), D2 (EP0127328A2), D3 (US 5,595,889), D4 (Abstract of JP03-147791), D5 (Abstract of JP03-147792), D6 (WO98/04715). These publications have been acknowledged by the Examiner.

Therefore, increasing protein activity by increasing concommitant DNA expression can be accomplished several ways, all well-known in the art, and fully described in the specification, such as placing the desired gene under the control of a stronger promoter, and/or increasing the copy number of the gene. These methods are exemplified in the specification particularly as relates to the novel SEQ ID NO: 4 and the concommitant DNA sequence, SEQ ID NO:3, and are documented by publications known in the art at the time of the invention for DNA expression of proteins in general. Therefore, applicants contend that the genus set forth in claim 37, and dependent claims 38 and 39 is actually quite small, and hence the description set forth of the genus in the specification is adequate, as the 2 representative species of promoter substitution and increased copy number could possibly comprise at least half the members of the genus, if not more. Nevertheless, the Examiner has failed to demonstrate a complete understanding of the limits of the genus throughout prosecution, and therefore, Appellants contend that the genus is fully and adequately described in the specification.

Claims 40, 41, and 42 merely add another protein species for which the DNA expression thereof is modified to increase the activity of said protein, and which renders the bacterium harboring said protein resistant to L-homoserine, as well. This protein is limited to the amino acid sequence in SEQ ID NO:2, and similar arguments to those made above apply to these claims as well. In fact, since these claims are all dependent on claim 37, even more limitations are added, rendering the claimed genus even smaller. Hence, the species set forth in the specification clearly are adequately described for the claimed genus, and appellants contend that these claims are fully and adequately described in the specification.

Independent claim 43 is similar to claim 37, in that an isolated bacterium which is modified to increase an activity of a protein which renders the bacterium harboring the protein L-threonine resistant as compared to a wild-type bacterium by increasing expression of a DNA coding for the protein; however the protein species is not specifically recited as in claim 37, but the DNA species is specifically recited as nucleotide numbers 187 to 804 of SEQ ID NO:3, or a DNA which hybridizes to this sequence under stringent conditions which are defined in the claim. Again, the dependent claims recite that the DNA expression is increased by increasing the copy number (claim 44) or by substitution of a promoter sequence (claim 45). Dependent claims 46, 47, and 48 are the parallels to claims 40, 41, and 42 in that they add the presence of another protein which renders the bacterium L-homoserine resistant.

Claim 43 actually encompasses a genus that is similar to claim 37, but claim 43 is limited to not the DNA which encodes the amino acid SEQ ID NO:4 (as in claim 37 - a large number of nucleotide sequences due to the redundancy of the genetic code), but is actually limited to the specific nucleotide sequence 187 to 804 of SEQ ID NO:3, or its hybidization derivatives under stringent conditions. Therefore, all the arguments made above can apply to these claims as well. Therefore, Appellants contend that claims 43-48 are also adequately described by the specification and urge that this rejection be withdrawn.

Therefore, the present claims do clearly allow the skilled artisan to recognize what has been invented and what is claimed, and that such is adequately described in the specification within the meaning of 35 USC 112, 1st paragraph.

C. The rejection of Claims 37-48 under 35 U.S.C. § 112, 1st paragraph, enablement, is in error

Claims 37-48 were rejected under section 112, 1st paragraph, alleging that the specification, while being enabling for a bacterium expressing the polypeptides of SEQ ID NO:2 or 4, or the polynucleotide of SEQ ID NO: 3, does not reasonably provide enablement for a bacterium expressing a polynucleotide comprising any deletion, substitution, insertion, or

addition variants of SEQ ID NO:4 or 2. This was the language of the original rejection set forth in the first Office Action mailed May 30, 2001. The claim language relating to "deletion, substitution, insertion, or addition variants of the above SEQ ID Nos. was deleted in the response to that first Office Action; however, the enablement rejection has continued to be made, although the literal scopes of the claims are limited to the particular species of bacterium expressing SEQ ID NO: 2 or 4, or the nucleotide sequence of SEQ ID NO:3, or its hybridization derivatives under stringent conditions. Notably, the claims reciting these protein and DNA species, Claims 16 and 17, have been allowed.

The Examiner maintains that the literal scope of the claimed bacteria is not enabled by the specification and the prior art according to the detailed analysis of the *Wands* factors, and undue experimentation would be required for a skilled artisan to make the entire scope of the claimed bacteria. Again, the Examiner acknowledges that increased DNA expression by transformation of a bacterium with an expression vector comprising said DNA or promoter substitution of an endogenous bacterial promotor with a well-known promoter are all well-known methods for increasing the level and therefore activity of a given protein. But, the Examiner states that the claims are so broad to encompass *Escherichia* bacteria having <u>any</u> modification that results in increased DNA expression of a protein that makes the bacteria L-threonine resistant and optionally where increased DNA expression is a result of increased DNA copy number (by any modification) or promoter substitution (by any promoter).

The Examiner has clearly not interpreted the claims correctly and, moreover, reference to the analysis of the *Wands* factors presented in the rejection of March 25, 2003, is moot since the claims have been amended, and those amendments entered, since that analysis was presented. The claims are not limited, or so broad in the Examiner's parlance, to just the increased DNA expression of a protein, but the increased DNA expression of the protein having the sequence of SEQ ID NO: 4, or the protein having the sequence of SEQ ID NO: 4 and 2, or the nucleotide sequence of SEQ ID NO. 3, or its hybridization derivatives under stringent conditions.

At pages 8-23 of the present specification, the Appellants fully describe appropriate methods of isolating, cloning, transforming bacteria, and culturing bacteria harboring the claimed

sequences. Moreover, on pages 23-25, the Appellants provide a detailed example showing how to clone the claimed sequences. In fact, the claims reciting the novel amino acid and DNA sequence (SEQ ID Nos. 2, 4, and 3, respectfully) have been indicted to be allowable. On pages 25-26, Appellants provide a screening method to identify bacteria containing viable clones, *i.e.*, by testing for L-threonine or L-homoserine resistance. And on pages 27-36, Appellants have provided examples demonstrating the operability of the present invention.

The claimed increased protein activity is accomplished by increasing the DNA expression of the claimed proteins, SEQ ID 2 and/or 4. Increasing the DNA expression is accomplished by increasing the copy number of the DNA in the cell, or by substitution of the promoter sequence of the gene encoding the protein in the chromosome of the bacterium. Various multi-copy vectors are disclosed on page 16, and methods of replacing a promoter sequence of a gene on a chromosome are well known in the art, as exemplified in the cited U.S. Patent No. 5,272,071. The Examiner has acknowledged that these are well-known methods in the art throughout the prosecution, *i.e.*, page 5 of the Office Action of January 30, 2004.

In the final rejection of March 25, 2003, the Examiner again reiterates that the specification and prior art fail to provide guidance for increasing protein activity by <u>any</u> modification to an E.coli. Again, the Examiner has misinterpreted the claims. The claims do not encompass <u>any modification</u> to an E.coli instead, their literal scopes encompass increasing protein activity by increasing DNA expression of SEQ ID NO.3, or increasing DNA expression of a DNA which encodes SEQ ID NO: 2 and/or 4. This is a huge difference. The Examiner continues on page 6 of the final rejection of March 25, 2003, to assert that the specification and prior art fail to provide guidance for increasing protein activity by altering the amino acid sequence of the protein of SEQ ID NO:2 or 4, and which alterations might result in a bacterium with increased activity of said protein. This assertion make no sense since the claims does not allow for alterations of the amino acid sequence. The DNA expression to be increased is that which encodes SEQ ID NO: 2 and/or 4; there is no other claim language which allows for alterations to the sequence. The Examiner has read the claim to be much broader than its definite, clear, and unambiguous meaning allows.

Appellants submit that one of skill in the art could obtain and use bacterium having increased protein activity, based on the disclosure provided in the specification, without undue experimentation, especially when the disclosure is augmented with the information known in the art. The specification discloses that increasing expression of the DNA coding for SEQ ID NO: 2 and/or 4 yields an increased activity in the bacterium expressing the DNA, thereby increasing L-homoserine or L-threonine (see page 6, line 22 – page 7, line 5). Therefore, the skilled artisan could screen or isolate other bacerium expressing the protein SEQ ID NO:4 by determining the resistance properties to L-homoserine or L-threonine (see page 7, lines 7-18); and/or amino acid production.

Therefore, Appellants submit that claims 37-48 are also adequately enabled by the specification and urge that this rejection be reversed.

D. Claims 37-48 are patentable and fully meet the written description and enablement prongs of 35 U.S.C. §112, 1st paragraph

For at least the reasons presented herein, each of the subject matters of Claims 37-48, taken as a whole, are patentable in view of the written description and enablement requirements of 35 U.S.C. §112, 1st paragraph. Accordingly, the rejection of each of Claims 37-48 under section 112, 1st paragraph is reversible error.

IX. Conclusion

For at least the foregoing reasons, Appellant respectfully submits that the subject matters of Claims 37-48, each taken as a whole, are patentable. Accordingly, Appellant respectfully requests reversal of the rejections of Claims 37-48 under section 112, 1st paragraph.

Respectfully submitted,

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APPENDIX: CLAIMS ON APPEAL

37. An isolated bacterium belonging to the genus *Escherichia*, wherein said bacterium is modified to increase an activity of a protein which makes the bacterium harboring the protein L-threonine resistant in comparison to a wild-type *Escherichia* bacterium by increasing expression of a DNA coding for the protein, and wherein the protein comprises the amino acid sequence of SEQ ID NO: 4.

38. The bacterium according to claim 37, wherein said bacterium is modified to increase an activity of the protein by increasing a copy number of a DNA coding for the protein.

39. The bacterium according to claim 37, wherein said bacterium is modified to increase an activity of the protein by substitution of a promoter sequence of the gene coding for the protein with a promoter sequence which functions efficiently in a bacterium belonging to the genus *Escherichia*.

40. The bacterium according to claim 37, wherein said bacterium is further modified to increase an activity of a protein which makes the bacterium harboring the protein L-homoserine resistant in comparison to a wild-type *Escherichia* bacterium by increasing expression of a DNA coding for the protein, and wherein the protein comprises the amino acid sequence of SEQ ID NO: 2.

41. The bacterium according to claim 37, wherein said bacterium is further modified to increase an activity of the protein which makes the bacterium harboring the protein L-homoserine-resistant in comparison to a wild-type *Escherichia* bacterium by increasing a copy number of a DNA coding for the protein, and wherein the protein comprises the amino acid sequence of SEQ ID NO: 2.

42. The bacterium according to claim 37, wherein said bacterium is further modified to increase an activity of the protein which makes the bacterium harboring the protein L-homoserine-resistant in comparison to a wild-type *Escherichia* bacterium by substitution of a promoter sequence of the gene coding for the protein with a promoter sequence which functions efficiently in a bacterium belonging to the genus *Escherichia*, and wherein the protein comprises the amino acid sequence of SEQ ID NO: 2.

43. An isolated bacterium belonging to the genus *Escherichia*, wherein said bacterium is modified to increase an activity of a protein which makes the bacterium harboring the protein L-threonine-resistant in comparison to a wild-type *Escherichia* bacterium by increasing expression of a DNA coding for the protein, and wherein the protein is encoded by a DNA which is defined in the following (a) or (b):

(a) a DNA which comprises the nucleotide sequence of nucleotide numbers 187 to 804 in SEQ ID NO: 3; or

(b) a DNA which hybridizes to nucleotides 187 to 804 in SEQ ID NO: 3 under a stringent condition, wherien the stringent condition is a condition in which washing is performed at 60°C, and at a salt concentration corresponding to 1 x SSC and 0.1% SDS.

44. The bacterium according to claim 43, wherein said bacterium is modified to increase an activity of the protein by increasing a copy number of a DNA coding for the protein.

45. The bacterium according to claim 43, wherein said bacterium is modified to increase an activity of the protein by substitution of a promoter sequence of the gene coding for the protein with a promoter sequence which functions efficiently in a bacterium belonging to the genus *Escherichia.*

46. The bacterium according to claim 43, wherein said bacterium is further modified to increase an activity of a protein which makes the bacterium harboring the protein L-homoserine resistant in comparison to a wild-type *Escherichia* bacterium by increasing expression of a DNA coding for the protein, and wherein the protein comprises the amino acid sequence of SEQ ID NO: 2.

47. The bacterium according to claim 43, wherein said bacterium is further modified to increase an activity of a protein which makes the bacterium harboring the protein L-homoserine resistant in comparison to a wild-type *Escherichia* bacterium by increasing a copy number of a

DNA coding for the protein, and wherein the protein comprises the amino acid sequence of SEQ ID NO: 2.

48. The bacterium according to claim 43, wherein said bacterium is further modified to increase an activity of a protein which makes the bacterium harboring the protein L-homoserine resistant in comparison to a wild-type *Escherichia* bacterium by substitution of a promoter sequence of the gene coding for the protein with a promoter sequence which functions efficiently in a bacterium belonging to the genus *Escherichia,* and wherein the protein comprises the amino acid sequence of SEQ ID NO: 2.